

Wouter Fransman · Roel Vermeulen · Hans Kromhout

## Dermal exposure to cyclophosphamide in hospitals during preparation, nursing and cleaning activities

Received: 9 July 2004 / Accepted: 11 November 2004 / Published online: 11 May 2005  
© Springer-Verlag 2005

**Abstract Objectives:** To determine levels of potential and actual dermal exposure to cyclophosphamide (CP) during performance of oncology-related tasks in hospitals and to investigate the relationship with potential sources and surface contamination levels of CP. **Methods:** Dermal exposure to CP was determined for tasks with potential exposure to CP: preparation of CP, decanting of patients' urine, washing of the patient, removal of bed sheets of treated patients and cleaning of patients' toilets on oncology wards. Exposure was assessed by the collection of nitrile and latex protective medical gloves (potential exposure), washing of hands (actual exposure), from cotton pads attached to (un)covered forearms (potential or actual exposure) and a wipe sample of the forehead (actual exposure). Bulk samples (i.e. application fluids and patients' excreta) and possible contact surfaces were monitored to assess the amount of CP available for dermal exposure. **Results:** Pharmacy technicians, oncology nurses and cleaning personnel showed actual and potential dermal exposure to CP during performance of their daily duties. Exposure occurred predominantly on the hands and sporadically on the forehead and forearms. Although all nurses used gloves during handling of patients' urine and sometimes during the other nursing tasks, skin underneath gloves was repeatedly contaminated. Results of tests on bulk and surface contamination samples confirmed that patients intravenously treated with CP excrete the unmetabolised drug, which could subsequently

lead to dermal exposure of hospital personnel. A clear relationship was found between dermal exposure levels and direct sources of exposure for all tasks, except for handling patients' urine. **Conclusions:** We demonstrated for the first time that actual dermal exposure to CP is common among oncology nurses working with patients treated with this anti-neoplastic drug. Pharmacy technicians and cleaning personnel, on the other hand, are potentially exposed to CP, and protection provided by gloves seemed to be sufficient.

**Keywords** Anti-neoplastic drugs · Cyclophosphamide · Dermal exposure · Hospital · Nurses · Pharmacy technicians

### Introduction

Occupational exposure to anti-neoplastic agents has been proven to cause reproduction toxic effects (Selevan et al. 1985; Stücker et al. 1990) as well as mutagenic activity in urine, and chromosomal aberrations and sister chromatid exchange in lymphocytes (Waksvik et al. 1981; Pohlová et al. 1986; Milkovic-Kraus and Horvat 1991; Sardas et al. 1991; Goloni-Bertollo et al. 1992; Sessink et al. 1994a, 1995). The pathway through which hospital personnel are exposed to these hazardous drugs is not known, but dermal exposure has been suggested to be the main route of exposure (McDevitt et al. 1993; Sessink et al. 1992b, 1994b; Kromhout et al. 2000). Studies that focussed on measuring the dermal route of exposure found gloves to be contaminated with anti-neoplastic agents during preparation and administration of these drugs (Sessink et al. 1994b, 1997; Minoia et al. 1998). Subsequently, this has led to the introduction of closed infusion systems, increased awareness of pharmacy technicians and nurses of the potential hazards, and the subsequent safer handling of highly concentrated anti-neoplastic drugs during preparation and administration. However, little attention has been paid

W. Fransman · R. Vermeulen · H. Kromhout (✉)  
Environmental and Occupational Health Division,  
Institute for Risk Assessment Sciences (IRAS),  
Utrecht University, PO Box 80176, 3508 TD  
Utrecht, The Netherlands  
E-mail: h.kromhout@iras.uu.nl  
Tel.: +31-0-30-2539440  
Fax: +31-0-30-2535077

R. Vermeulen  
Division of Cancer Epidemiology and Genetics,  
Occupational and Environmental Epidemiology Branch,  
National Cancer Institute, Rockville, Maryland, USA

to other potential exposure moments during nursing and cleaning tasks involving treated patients. In a recent pilot study on dermal exposure to cyclophosphamide (CP) in hospitals, we found pharmacy technicians, oncology nurses and cleaning personnel to be exposed to CP via the dermal route during performance of their daily duties (Fransman et al. 2004).

The aims of this study were to determine levels of potential and actual dermal exposure to CP during performance of oncology-related tasks in hospitals and to study the relationship of potential dermal exposure levels with potential sources and surface contamination levels of CP. To do so we measured in four hospitals the potential and actual dermal exposure to CP of (1) pharmacy technicians during preparation of CP; (2) oncology nurses during: handling of CP-treated patients' urine, washing of CP-treated patients, and removal of their bed sheets; (3) cleaning personnel during cleaning of CP-treated patients' toilets. Dermal exposure was measured at the hands, forehead, and forearms, because results of a pilot study did not find body locations other than these to be frequently contaminated with CP during the five tasks observed (Fransman et al. 2004). Bulk samples (application fluids and patients' excreta) and surface contamination samples were collected to elucidate and quantify the strength of potential sources of exposure.

## Materials and methods

CP is one of the many anti-neoplastic agents that are frequently used in Dutch hospitals and for which sensitive analytical techniques are available. Therefore, exposure to CP was chosen as a measure of exposure to anti-neoplastic drugs. Dermal exposure to CP was repeatedly measured in four hospitals during the performance of five tasks: (1) preparation of CP, (2) handling of CP-treated patients' urine, (3) washing of CP-treated patients, (4) removal of sheets from CP-treated patients' beds and (5) cleaning of CP-treated patients' toilets. Measurements on oncology wards were taken the morning after CP had been intravenously administered to the patient, when one nurse successively performed the three nursing tasks (handling urine, washing the patient and removing bed sheets) related to the same patient. This study was approved by the Dutch ethics committee (University Medical Centre, Utrecht, The Netherlands), and all study subjects gave written informed consent prior to their inclusion in the study.

### Dermal exposure measurements

Medical (latex or nitrile) gloves (if used) were collected (left and right glove pooled as one sample), after performance of the task, as a measure of potential exposure to the hands. If a double pair of gloves was used, only the outer pair was collected. Subsequently, both hands

were washed in a polyethylene bag with 250 ml of 10% isopropanol solution, to enable us to assess actual exposure of the hands (Brouwer et al. 2000), of which approximately 40 ml was collected in a 50-ml polypropylene tube. Cotton pads (10×10 cm) were attached with surgical tape to the outside of protective clothing at the forearms (left and right) of pharmacy technicians. In contrast to pharmacy technicians, nurses' and cleaners' forearms were not covered by clothing, so pads were attached directly to the skin of the forearms. The backs of all cotton pads were laminated with polyethylene to avoid contamination from the clothing or skin to the pad. Pads from the forearms (left and right) were pooled and analysed as one sample. Since it was not desirable (for normal patient–nurse interactions) for a cotton pad to be attached to the forehead, a wipe sample of the forehead (5×3 cm) was taken at the end of the task with two tissues and 10 ml of 10% isopropanol solution. Pads, gloves and forehead wipe samples were stored in polyethylene containers (250 ml) at –20 °C till required for analysis.

### Bulk and surface contamination samples

In addition to potential and actual dermal exposure measurements, bulk and surface contamination samples were taken to assess the amount of CP to which hospital personnel could potentially be exposed (i.e. source strength) during the tasks performed. The concentration of CP was determined in: patients' urine, washing water (+ soap) after the patient had been washed, and cleaning water (+ detergent) after a patient's toilet had been cleaned. Using two tissues and 20 ml of 0.03 M sodium hydroxide solution we took wipe samples of the total surface of: (1) the front edge of safety cabinets in hospital pharmacies, (2) the outside of infusion bags and syringes prepared in hospital pharmacies, (3) outer urinals and bedpans before they had been rinsed, (4) inner bedpans after they had been rinsed in a urinal/bedpan-washer, (5) toilet seats after they had been cleaned, and (6) mop rods after the toilet floor had been scrubbed. Furthermore, cleaning cloths, washcloths, an excised section of towels (100 cm<sup>2</sup>), two excised sections of bed sheets (2×100 cm<sup>2</sup>, corresponding to the back and lower abdomen of the patient), and an excised section of the top side of pillowcases (100 cm<sup>2</sup>) were collected for analysis of CP contamination. Before sheets were removed from the bed by the oncology nurse, the top side of the pillow and two sections of the bed sheet were vacuum cleaned to see whether CP (attached to textile fibres and/or other particles) could potentially be released from the sheet or pillowcase thereby causing exposure by inhalation. Dust samples were collected on glass fibre filters (Ø 70 mm) with a sampling nozzle manufactured by ALK Laboratories (Horsholm, Denmark) and a 1,000 W Rowenta vacuum cleaner (van Strien et al. 1994). The two sections that were cut out from the bed sheet were located directly next to the two

sections of the sheet that were vacuum cleaned. All samples were stored at  $-20^{\circ}\text{C}$  till required analysis.

### Analysis of samples

Pad, glove, wipe and cloth samples were extracted with 160 ml (dust filters were extracted with 40 ml) of 0.03 M sodium hydroxide solution and subsequently analysed for CP with gas chromatography–tandem mass spectrometry (GC–MSMS) as described previously (Sessink et al. 1993). Liquids (i.e. handwash, urine, washing water and cleaning water) were directly analysed for CP by the same GC–MSMS method. The analytical method described had a limit of detection (LOD) of 0.1 ng/ml. The analytical-standard CP was purchased from Asta-Medica and was of the highest purity obtainable ( $>97\%$ ).

### Quality assurance

For each kind of sampling material one field blank sample per task was taken. None of the blank dermal exposure samples was above the instrument detection limit (IDL). Four blank bulk and wipe samples appeared to be on or just above the IDL of 0.1 ng/ml (two wipe samples, 0.10 ng/ml and 0.16 ng/ml; washing water, 0.18 ng/ml; vacuum sample, 0.30 ng/ml). Therefore, LOD and limit of quantification (LOQ) could not be justifiably calculated. The LOD was thus treated as equivalent to the IDL of 0.1 ng/ml. Average recovery efficiencies of CP for the analysed dermal sampling matrices were 107% (SD=8%) for handwash solution, 110% (SD=11%) for pads and 117% (SD=22%) for forehead wipe samples, as previously determined (Fransman et al. 2004). The results of those sampling matrices were, therefore, not corrected for recovery efficiency. Results of glove samples were corrected for an average recovery estimated at 58% (SD=17%) for latex gloves in an earlier study (Sessink et al. 1992a).

### Statistical analysis

Data were analysed with SAS statistical software (version 8.02; SAS Institute, Cary, N.C., USA). In situations where sample values were below the LOD, 0.5LOD was substituted for sample values (Hornung and Reed 1990). Dermal exposure levels appeared to approximate a lognormal rather than a normal distribution, so summary statistics are presented both as arithmetic and geometric mean levels. Differences between hospitals in dermal exposure and bulk and surface contamination levels were tested with a general linear model (PROC GLM) in SAS. In this model, the hospital was treated as an independent variable. The glove level of protection was calculated by dividing the CP contamination on gloves by the CP contamination on gloves plus the CP contamination on the bare skin of hands (glove

protection =  $[\text{CP}_{\text{gloves}}/(\text{CP}_{\text{gloves}} + \text{CP}_{\text{handwash}})]$ ). Measurements for gloves below the LOD and handwash below the LOD were not included in the calculation of the average glove protection level. When only one of the two sampling matrices (gloves or handwash) was below the LOD, glove protection was calculated from 0.5LOD for the value below LOD. Pearson correlation coefficients were calculated from natural log-transformed data to enable us to examine the relationship between the administered CP dose and CP levels in patients' excreta the morning after administration and to study the interrelationship between the various sources and potential dermal exposure levels on the hands.

## Results

Task characteristics by hospital are presented in Table 1. Hospitals 1 and 2 are academic hospitals, hospitals 3 and 4 are district hospitals. In hospital 2, measurements were taken in the haematology department, where CP was administered in higher concentrations than in the oncology departments in the other three hospitals. Gloves were worn at all times during CP preparation (latex gloves), the handling of CP-treated patients' urine (latex or nitrile gloves) and the cleaning of CP-treated patients' toilets (latex or nitrile gloves). During the washing of CP-treated patients and removal of their bed sheets, gloves were worn as a rule in hospital 2 only and not in any of the other hospitals. The decision of which types of gloves were to be used was made by the hospital and differed between hospital and task (Table 1).

Table 2 shows the number of detectable samples ( $n > \text{LOD}$ ) and average exposure levels per body location per task in nanogrammes per task (ng/task). Results from forearms and forehead reflect the amount (mass) of CP found on the sampling location only (i.e. 200 and 15 cm<sup>2</sup>) and were not extrapolated to estimate exposure to the entire body location (i.e. forearms and forehead). For all tasks CP contamination was found mainly on the hands (gloves and handwash samples) and sporadically on forehead and forearms.

### Pharmacy technicians

Preparation of CP was performed in hospital pharmacies in safety cabinets (laminar down flow) by trained pharmacy technicians wearing an apron, surgical mask, hair cover (a hood was used in hospital 3) and latex surgical gloves (27% wore two pairs of gloves). During preparation of CP, all gloves were contaminated with CP [geometric mean (GM)=106.1 ng/task], while hands underneath gloves appeared to be contaminated only once (4%  $> \text{LOD}$ ) (Table 2). This indicates that gloves protect hands well during CP preparation. Sporadically, the forehead (13%  $> \text{LOD}$ ) and forearms (4%  $> \text{LOD}$ ) were contaminated. The front edge of safety cabinets (46%  $> \text{LOD}$ ; GM = 20.9 ng) and the outside of infusion

**Table 1** Glove use and range of CP dose administered per hospital during the measurement period

Parameter	Academic hospitals		District hospitals	
	Hospital 1	Hospital 2	Hospital 3	Hospital 4
Preparation				
Glove use	–	100% 1 pair (latex)	90% 1 pair (latex), 10% 2 pairs (latex)	100% 2 pairs (latex)
Range in amount of prepared CP	–	1,000–5,976 mg	900–4,200 mg	2,000–12,000 mg
Handling urine				
Glove use	100% 1 pair (nitrile)	100% 1 pair (nitrile)	100% 1 pair (latex)	100% 1 pair (latex)
Range in administered CP dose	150–3,750 mg	3,000–6,000 mg	800–1,200 mg	1,870–2,150 mg
Washing patient				
Glove use	No gloves used	100% 1 pair (nitrile)	No gloves used	60% no gloves used, 40% 1 pair (latex)
Range in administered CP dose	150–3,750 mg	3,000–6,000 mg	800–1,200 mg	1,720–2,150 mg
Removing bed sheets				
Glove use	No gloves used	100% 1 pair (nitrile)	No gloves used	No gloves used
Range in administered CP dose	150–3,750 mg	3,000–6,000 mg	800–1,200 mg	1,720–2,150 mg
Cleaning toilet				
Glove use	100% 2 pairs (nitrile)	100% 1 pair (latex)	100% 1 pair (latex)	100% 1 pair (latex)
Range in administered CP dose	150–3,750 mg	4,320–5,220 mg	900–1,200 mg	1,720–1,930 mg

bags or syringes (25% > LOD; GM = 16.2 ng) appeared to be contaminated with CP (Table 3). No differences between hospitals in potential dermal exposure and surface contamination were found for preparation of CP. The possible extra protection of wearing two pairs of gloves could not be determined because only one hand-wash sample was above the LOD during preparation.

### Oncology nurses

Oncology nurses performed three nursing tasks (handling CP-treated patients' urine, washing CP-treated patients and removing their bed sheets) on oncology wards. All nurses used examination gloves (46% nitrile and 54% latex) while handling CP-treated patients' urine, 36% of nurses used gloves (80% nitrile and 20% latex) while washing CP-treated patients and 29% of nurses used gloves (nitrile) during removal of the bed sheets of CP-treated patients. During all three nursing tasks on oncology wards (handling urine, washing patients, removing bed sheets) gloves and the skin of hands appeared to be repeatedly contaminated with CP. Sporadically, forehead and forearms were contaminated with CP. Not surprisingly, the nursing task with the least contained sources of exposure (washing patients) showed most detectable samples on the forehead and forearms (25% and 11% above the LOD, respectively), while the nursing task with the best contained source of exposure (handling urine) showed the least detectable samples on the forehead and forearms (8% and 0% above the LOD, respectively) (Table 2). During the handling of CP-treated patients' urine, gloves were worn by all nurses. Nevertheless, the skin underneath gloves appeared to be contaminated with CP several times, indicating poor glove protection (GM = 38.3%; range 9.0–91.0%). It is noteworthy that eight handwash samples appeared to be contaminated, while CP

contamination on concurrent gloves during handling of urine was not detectable, suggesting that the skin might not be contaminated through penetration of gloves. Gloves were not regularly worn during the washing of CP-treated patients and removal of their bed sheets, which is reflected in the CP contamination found on the skin of hands (handwash samples). When gloves were used during the washing of CP-treated patients, protection of gloves was reasonably good (GM = 81.7%; range 39.8–97.1%). During the removal of bed sheets of CP-treated patients, the use of gloves seemed to be less effective (GM = 38.9%; range 7.7–79.9%) (Table 2). No differences between hospitals in potential or actual dermal exposure levels during nursing tasks were found.

During all three nursing tasks in oncology wards multiple potential exposure sources of CP were present. Patients' urine contained high levels of CP (GM = 14,696 ng/ml), and the outside of all urinals and bedpans appeared to be contaminated with CP (GM = 153.9 ng). One out of five bedpans appeared still to be contaminated with low levels of CP after being washed (GM = 10.9 ng). The water, cloth and excised section of the towel used for washing CP-treated patients were all frequently contaminated with CP (GM<sub>water</sub> = 43.6 ng/ml; GM<sub>cloth</sub> = 2,135 ng; GM<sub>towel</sub> = 436.2 ng). Furthermore, excised sections of CP-treated patients' pillowcases and bed sheets appeared to be repeatedly contaminated with CP (GM<sub>pillowcase</sub> = 97.8 ng; GM<sub>sheet, patient's back</sub> = 48.8 ng; GM<sub>sheet, patient's abdomen</sub> = 64.0 ng) as well as vacuum samples taken from pillows and bed sheets (GM<sub>pillow</sub> = 142.2 ng; GM<sub>sheet</sub> = 78.4 ng) (Table 3).

### Cleaning personnel

Cleaners (who were not part of the nursing staff) cleaned CP-treated patients' toilets using examination gloves

**Table 2** Average task duration, CP contamination levels on the hands, forehead, forearms (ng/task) and protection of gloves (%) per task.  $LOD_{gloves}$  (0.1 ng/ml×160 ml)/58% = 27.6 ng/task;  $LOD_{handwash}$  0.1 ng/ml×250 ml = 25 ng/task;  $LOD_{forehead}$  0.1 ng/ml×160 ml = 16 ng/task;  $LOD_{forearms}$  0.1 ng/ml×160 ml = 16 ng/task (*N* number of measurements per task, *N* > *LOD* number of measurements above the limit of detection, *AM* arithmetic mean, *GM* geometric mean)

Pharmacy technicians	Preparation			Washing patient			Removing bed sheets		
	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>	AM	GM	Range	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>
Task duration (min)	26			23.8	17.2	7.0–165.0			
Potential hands <sup>a</sup> (ng/task)	26	12	46%	644.0	106.1	26.3–5,433.2			
Actual hands <sup>b</sup> (ng/task)	26	1	4%	13.6	13.1	12.5–40.0			
Forehead (wipe) (ng/task)	16 <sup>c</sup>	2	13%	9.5	8.9	8.0–24.0			
Forearms (pads) (ng/task)	26	1	4%	153.1	10.1	8.0–3,780.8			
Protection of gloves (%) <sup>d</sup>	12			93.4%	93.0%	74.2–99.8			
Oncology nurses	Handling urine			Washing patient			Removing bed sheets		
	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>	AM	GM	Range	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>
Task duration (min)	26			5.7	5.5	5.0–10.0			
Potential hands <sup>a</sup> (ng/task)	26	14	54%	56.4	44.8	26.3–202.6			
Actual hands <sup>b</sup> (ng/task)	26	10	38%	28.6	20.4	12.5–140.0			
Forehead (wipe) (ng/task)	26	2	8%	9.5	8.7	8.0–40.0			
Forearms (pads) (ng/task)	26	0	0%	8.0	8.0	–			
Protection of gloves (%) <sup>d</sup>	14			46.5%	38.3%	9.0–91.0			
Cleaning personnel	Cleaning toilet			Washing patient			Removing bed sheets		
	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>	AM	GM	Range	<i>N</i>	<i>N</i> > <i>LOD</i>	Percentage AM > <i>LOD</i>
Task duration (min)	19			14.2	13.0	5.0–25.0			
Potential hands <sup>a</sup> (ng/task)	19	10	53%	194.6	82.1	13.8–800.0			
Actual hands <sup>b</sup> (ng/task)	19	0	0%	12.5	12.5	–			
Forehead (wipe) (ng/task)	19	2	11%	9.6	8.9	8.0–24.0			
Forearms (pads) (ng/task)	19	3	16%	12.0	9.9	8.0–49.6			
Protection of gloves (%) <sup>d</sup>	10			100% <sup>e</sup>	100% <sup>e</sup>	80.7–98.5			

<sup>a</sup>Potential hands = handwash + gloves (if used)

<sup>b</sup>Actual hands = handwash

<sup>c</sup>Ten measurements were not taken because forehead was covered with a hood

<sup>d</sup>Glove protection =  $[(CP_{gloves}/(CP_{gloves} + CP_{handwash}))]$ ; measurements with gloves < *LOD* and handwash < *LOD* were not included in calculating the average glove protection level; when only one of the two (gloves or handwash) was below *LOD*, the glove protection was calculated using 0.5*LOD* for the value below *LOD*

<sup>e</sup>Because none of the handwash samples was above *LOD*, the glove protection was set to 100%

**Table 3** Median CP concentrations in bulk and surface contamination samples per task. LOD=0.1 ng/ml×160 ml = 16 ng; LOD<sub>vacuum</sub> = 0.1 ng/ml×40 ml = 4.0 ng; LOD<sub>liquids</sub> = 0.1 ng/ml. *N* number of measurements per task

Parameter	<i>N</i>	<i>N</i> > LOD	Percentage > LOD	AM	GM	Range	Median volume (ml) or total surface area (cm <sup>2</sup> )
<i>Preparation</i>							
CP solution used during preparation <sup>a</sup> (ng/ml)	26	26	100%	2.0·10 <sup>7</sup>	2.0·10 <sup>7</sup>	–	100 ml
Front edge safety cabinet (ng)	26	12	46%	95.1	20.9	8.0–1,597	1,170 cm <sup>2</sup>
Outside of infusion bag/syringe (ng)	20	5	25%	205.2	16.2	8.0–3,299	278 cm <sup>2</sup>
<i>Handling urine</i>							
Urine (ng/ml)	26	26	100%	16,192	14,696	2,600–28,600	240 ml
Outer urinal/bedpan (before washing) (ng)	11	11	100%	395.9	153.9	16.0–1,378	1,400 cm <sup>2</sup>
Inside bedpan (after washing) (ng)	5	1	20%	13.8	10.9	8.0–36.8	925 cm <sup>2</sup>
<i>Washing patient</i>							
Washing water (ng/ml)	28	28	100%	80.9	43.6	0.9–317.4	2,250 ml
Washing cloth (ng)	28	28	100%	5,625	2,135	36.8–31,152	560 cm <sup>2</sup>
Towel (100 cm <sup>2</sup> section) (ng)	28	25	89%	1,303	436.2	8.0–7,936	4,416 cm <sup>2</sup>
<i>Removing bed sheets</i>							
Pillowcase (100 cm <sup>2</sup> section) (ng)	28	20	71%	258.7	97.8	8.0–910.4	5,082 cm <sup>2</sup>
Sheet: back of patient <sup>b</sup> (100 cm <sup>2</sup> section) (ng)	28	21	75%	110.1	48.8	8.0–712.0	7,200 cm <sup>2</sup>
Sheet: abdomen of patient <sup>b</sup> (100 cm <sup>2</sup> section) (ng)	28	22	79%	179.0	64.0	8.0–1,971	7,200 cm <sup>2</sup>
Vacuum samples: pillowcase (ng)	28	28	100%	434.9	142.2	6.0–3,057	5,082 cm <sup>2</sup>
Vacuum samples: sheet (2×100 cm <sup>2</sup> sections) (ng)	28	28	100%	147.8	78.4	9.2–751.2	28,800 cm <sup>2</sup>
<i>Cleaning toilet</i>							
Cleaning water (ng/ml)	11	4	36%	1.14	0.22	0.05–4.38	3,500 ml
Cleaning cloth (ng)	17	14	82%	6,939	1,171	8.0–43,991	1,600 cm <sup>2</sup>
Mop rod (ng)	5	3	60%	19.5	15.6	8.0–46.4	1,400 cm <sup>2</sup>
Toilet seat after cleaning (ng)	18	17	94%	1,920	458.5	8.0–8,234	1,900 cm <sup>2</sup>

<sup>a</sup>CP concentration in solution is based on the reported formulation by pharmacy technicians

<sup>b</sup>Corresponds to 1/4 of the bed sheet

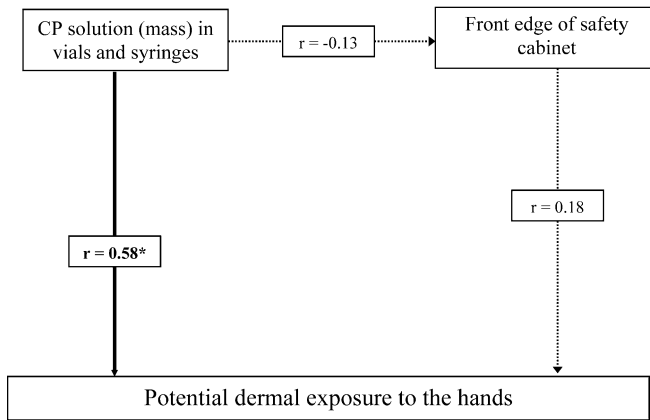
(26% nitrile and 74% latex), of which 26% used a double pair of gloves. During the cleaning of CP-treated patients' toilets, gloves of cleaning staff appeared to be repeatedly contaminated with CP, but not the skin of hands underneath gloves, which indicates that gloves protect the hands well during cleaning (Table 2). The cleaning cloth and mop rod were frequently contaminated with CP after the task was performed (GM<sub>cloth</sub> = 1,171 ng; GM<sub>mop rod</sub> = 15.6 ng), and the water used for cleaning appeared only to be contaminated when the cloth was rinsed out in the cleaning water (and not when this did not happen) (GM<sub>water</sub> = 0.22 ng/ml). The toilet seat appeared to be still highly contaminated with CP after it had been cleaned (GM 458.5 ng), indicating that the cleaning procedure used was not adequate to remove all contamination from CP-treated patients' toilets. Gloves and cleaning cloths of cleaning staff in hospital 2 appeared to be significantly ( $P < 0.05$ ) more highly contaminated than in the other three hospitals. However, in hospital 2 (in contrast to the other hospitals), the toilet was located inside the bathroom, so gloves and cloths were used for cleaning the entire bathroom, which could have caused higher contamination levels.

#### Relationship between exposure levels and potential sources

The relations between potential dermal exposure levels and potential sources of exposure are illustrated in

Figs. 1, 2 and 3 for pharmacy technicians, oncology nurses and cleaning personnel, respectively. Figure 1 shows that direct exposure from the source is the most likely dermal exposure pathway during preparation of CP ( $r = 0.58$ ;  $P = 0.002$ ;  $N = 26$ ), and probably not the indirect exposure route through surface contamination. During the handling of patients' urine neither direct contact with the contaminated urine ( $r = -0.06$ ;  $P = 0.76$ ;  $N = 26$ ) nor contact with the contaminated urinal or bedpan ( $r = -0.07$ ;  $P = 0.83$ ;  $N = 11$ ) seems to be the main pathway through which exposure occurs. During the washing of treated patients, direct contact with the washcloth ( $r = 0.78$ ;  $P < 0.0001$ ;  $N = 28$ ), the contaminated water ( $r = 0.58$ ;  $P = 0.001$ ;  $N = 28$ ) and towel ( $r = 0.71$ ;  $P < 0.0001$ ;  $N = 28$ ) seem to be closely related to potential dermal exposure to the hands. During removal of bed sheets, potential dermal exposure levels were more strongly correlated with CP levels in sheets (i.e. excised section of sheet corresponding to patient's back + excised section of sheet corresponding to patient's abdomen) ( $r = 0.67$ ;  $P = 0.0001$ ;  $N = 28$ ) than CP levels in pillowcases ( $r = 0.22$ ;  $P = 0.27$ ;  $N = 28$ ). The correlation between CP levels in pillows and CP levels in vacuum samples from pillows was moderate ( $r = 0.36$ ;  $P = 0.057$ ;  $N = 28$ ), just as the correlation between CP levels in sheets and CP levels in vacuum samples from sheets ( $r = 0.55$ ;  $P = 0.002$ ;  $N = 28$ ). Figure 3 shows that during the cleaning of CP-treated patients' toilets, potential dermal exposure is most likely to come from the cleaning cloth ( $r = 0.66$ ;  $P = 0.0039$ ;  $N = 17$ ).

### Pharmacy technicians



\*  $P < 0.05$

**Fig. 1** Relationship between skin contamination with CP and potential sources of CP exposure for pharmacy technicians in hospital pharmacies during preparation of CP. Correlation between boxes is illustrated by Pearson correlation coefficients

CP concentration in water used for washing a CP-treated patient seemed to be moderately correlated with CP levels found in bed sheets corresponding to the

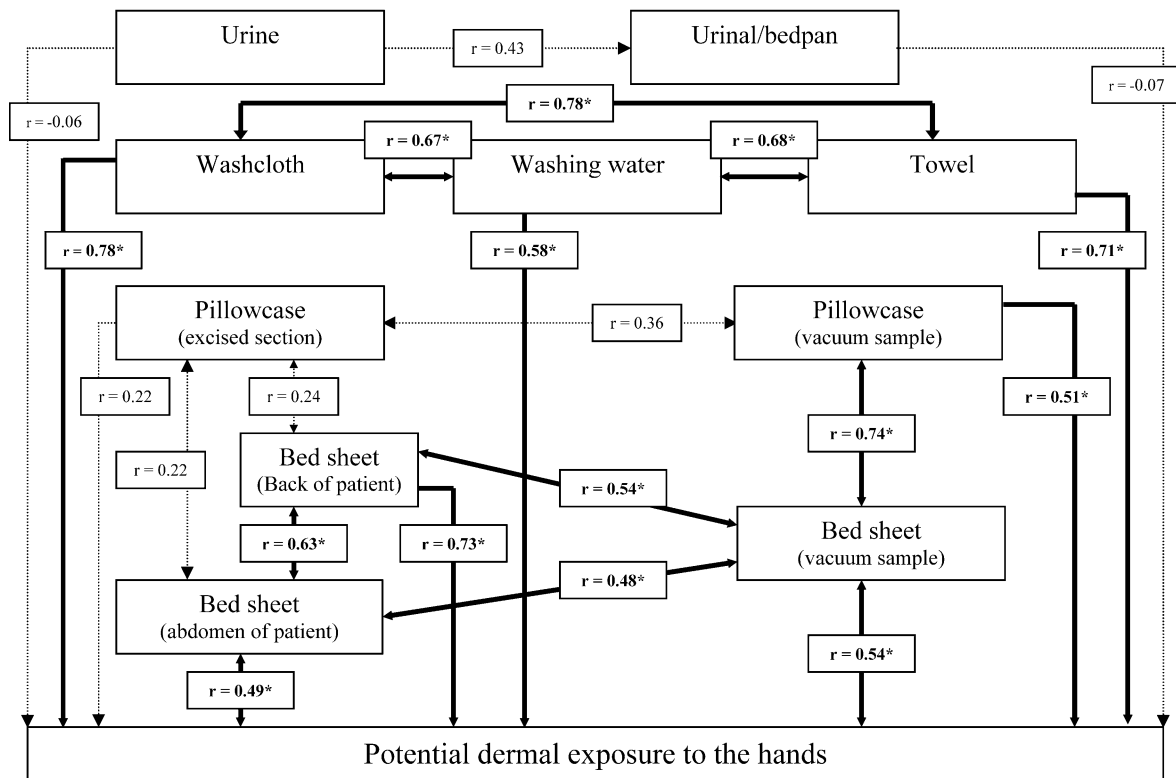
**Fig. 2** Relationship between skin contamination with CP and potential sources of CP exposure per task for oncology nurses on oncology wards during nursing tasks. Correlation between boxes is illustrated by Pearson correlation coefficients

patient's back ( $r = 0.56$ ;  $P = 0.002$ ;  $N = 28$ ), bed sheets corresponding to the patient's lower abdomen ( $r = 0.50$ ;  $P = 0.007$ ;  $N = 28$ ) and the vacuum sample taken from the sheet ( $r = 0.44$ ;  $P = 0.019$ ;  $N = 28$ ). This indicates that they share the same source of exposure (i.e. sweat of patient) or might indicate that the washing of CP-treated patients in bed could lead to transfer of CP contamination from washing water to the bed sheets.

### Discussion

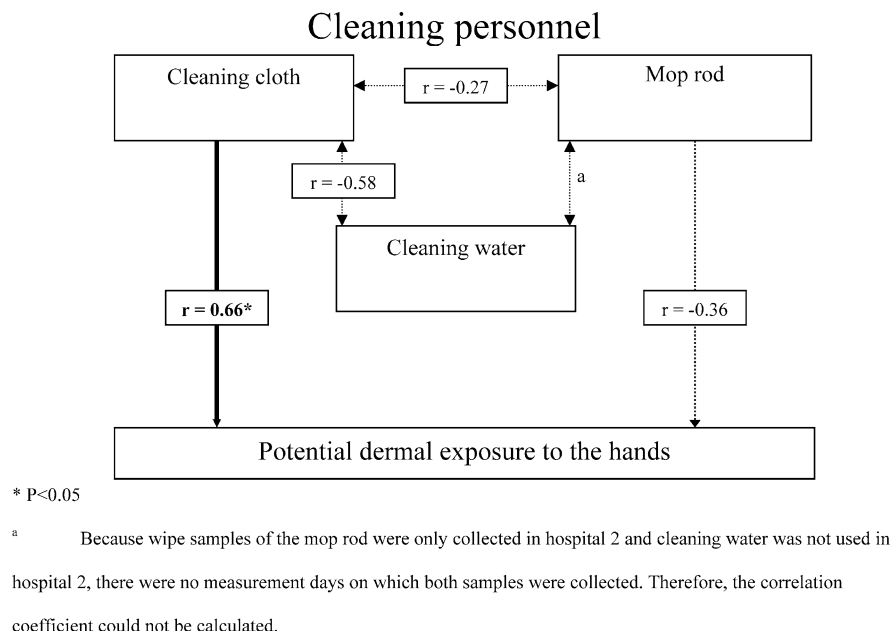
This study has clearly shown that pharmacy technicians, oncology nurses and cleaning personnel are potentially dermally exposed to CP during the performance of their daily duties. Exposure to CP occurred predominantly to hands, and sporadically to the forehead and forearms. Only oncology nurses appeared to be repeatedly exposed to CP on the skin of hands. Highest actual dermal exposure levels were found during the washing of CP-treated patients and removal of their bed sheets. This is due to the fact that gloves were generally not used during these tasks. The use of gloves during the washing of CP-treated patients significantly lowered the contamination on the hands underneath gloves by a factor of 4. During removal of bed sheets of CP-treated patients, the use of gloves lowered the contamination on the skin of hands by only 1.6-fold. Although gloves were worn by all nurses during handling of CP-treated

### Oncology nurses



\*  $P < 0.05$

**Fig. 3** Relationship between skin contamination with CP and potential sources of CP exposure for cleaning personnel on oncology wards during the cleaning of patients' toilets. Correlation between boxes is illustrated by Pearson correlation coefficients



patients' urine, bare hands underneath gloves were repeatedly contaminated, even when CP was not detected on gloves, suggesting that bare skin of hands might not be contaminated through penetration of gloves.

Although most CP contamination was found on the hands, uncovered forehead and forearms of nurses and cleaning personnel appeared to be contaminated sporadically. The task with the least contained sources of exposure (washing patient) had most detectable samples on the forehead and forearms, probably due to direct contact with droplets of washing water. Also, the cleaning of patients' toilets sometimes resulted in CP contamination on the forehead and forearms.

In this study several sampling techniques (gloves, handwash, skin wipe and patches) were used to assess dermal exposure. Since these methods have different sampling efficiencies, direct comparisons should be interpreted with caution. Surrogate skin sampling techniques (gloves and patches) are known to overestimate exposure. Therefore, exposure to forearms could have been overestimated; however, only small amounts of CP were detected on forearms. The possible overestimation of glove contamination could have led to an overestimation of glove protection. Furthermore, because the entire gloves were analysed, the CP contamination could have (partly) been on the inside of gloves and not on the outside and would, therefore, reflect actual rather than potential exposure to the hands. This indicates that actual exposure to the hands might have been somewhat higher than presented here and glove protection levels could have been overestimated. In addition, the correcting of glove sample results for the low recovery efficiency of glove samples (58%) could have potentially resulted in an overestimation of the level of protection from gloves. Therefore, the ratio was calculated between

the two different glove protections—unadjusted for the recovery and adjusted for the 58% recovery—and ranged from 0.73 (handling patients' urine) to 0.96 (preparation of CP). So, although the adjustment for recovery efficiency could have led to a small overestimation of the glove protection level, the conclusion about poor protection from gloves during the handling of patients' urine and removal of bed sheets and better protection from gloves during preparation, washing patients and cleaning patient toilets, remains. The recovery of 58%, used in this study, was determined in an earlier study (Sessink et al. 1992a) using latex gloves of one specific brand (Ansell Gammex pre-powdered sterile latex hypoallergenic surgical gloves). In our study, numerous different glove types were used in the four hospitals. Thus, we were unable to estimate the recovery efficiencies of all these different glove types and, therefore, had to assume that recovery efficiencies were equal between different glove types, which might have resulted in some exposure misclassification.

Bulk and surface contamination levels show that multiple sources of exposure were present during all observed tasks. Based on the correlation between dermal exposure levels and bulk and surface contamination levels and dermal exposure levels on the hands, the pathway through which dermal exposure occurs per task could be hypothesised for pharmacy technicians, oncology nurses and cleaning personnel. During CP preparation, the pathway through which dermal exposure occurs appeared to be direct contamination from the source (droplets from vials and syringes containing CP, or from possible contamination on the outside of vials (Mason et al. 2003) onto the gloves. During the handling of urine, neither direct contact with the urine nor contact with the contaminated outside of urinals or bedpans seemed to be the route of dermal exposure,

which suggests that dermal exposure during the handling of patients' urine probably occurs through accidental splashes and, as such, has no direct relationship to the source strength. During the washing of treated patients, direct contact with the washcloth and contact with the contaminated water and towel appeared to be correlated with potential dermal exposure to the hands, which corroborates the notion that continuous contact with the contaminated cloth and immersion of the hands in the water leads to dermal exposure on hands. During the removal of bed sheets, the correlation between dermal exposure levels and CP levels in bed sheets seemed to be reasonably good, which implies that contact with contaminated bed linen could cause exposure to CP. Interestingly, CP was detected in all vacuum samples from pillowcases and bed sheets. It is, therefore, conceivable that textile fibres (or other particles) contaminated with CP could become airborne while bed linen is removed from treated patients' beds. This observation supports the findings in an earlier study, where airborne levels of CP were detected in a patient's room in a nursing clinic, while administration of CP had taken place somewhere else (Kromhout et al. 2000). During the cleaning of CP-treated patients' toilets, direct contact with the cleaning cloth seemed to be the main route of dermal exposure.

The results are consistent with pilot study results (Fransman et al. 2004), showing the same pattern of dermal exposure to CP for pharmacy technicians, oncology nurses and cleaning personnel during performance of their daily tasks. Bulk and surface contamination levels are consistent with pilot results in that they confirm that patients intravenously treated with CP, excrete CP unmetabolised via their excreta (i.e. urine, sweat) the morning after the drug had been administered. Glove contamination levels found during preparation of CP in this study were on average 8–25 times lower than those found in earlier studies where similar amounts of CP were prepared (Sessink et al. 1994b, 1997; Minoia et al. 1998), suggesting that better awareness of pharmacy technicians working with anti-neoplastic agents has reduced potential exposure levels. This is supported by the strong (25–6,000 times) reduction in contamination of safety cabinets found during preparation in comparison with earlier studies (McDevitt et al. 1993; Minoia et al. 1998; Connor et al. 1999).

In conclusion, pharmacy technicians, oncology nurses and cleaning personnel are potentially dermally exposed to CP during performance of their tasks. Exposure occurred mainly to the hands and sporadically to the forehead and forearms. The use of protective gloves by pharmacy technicians during CP preparation and by cleaning personnel during the cleaning of patients' toilets seems to be successful in reducing actual skin exposure underneath gloves. Effectiveness of gloves during nursing tasks varied greatly between tasks and appeared not to be sufficient for all tasks. Nevertheless, there is good reason for using gloves while nursing patients treated with CP, because patients' excreta (urine,

sweat) are highly contaminated with CP, and direct or indirect contact with patients' excreta (e.g. urine, sweat, faeces, vomit) could, therefore, lead to significant exposure. Because CP is found in the patient's toilet and room, labelling of treated patients' toilets and treated patients' rooms seems to be essential, to indicate possible contamination with anti-neoplastic drugs and to warn people before they enter those areas.

**Acknowledgements** This study was partly facilitated by the RI-SKOFDERM-project, supported by the European Commission Contract QLK4-CT-1999-01107. The authors are indebted to the management, workers and patients of the four hospitals for their participation in this study. The participating hospitals and the Dutch Ministry of Social Affairs and Employment, as part of a covenant with academic hospitals, financed parts of the study.

## References

- Brouwer DH, Boeniger MF, van Hemmen JJ (2000) Hand wash and manual skin wipes. *Ann Occup Hyg* 44:501–510
- Connor TH, Anderson RW, Sessink PJM, Broadfield L, Power LA (1999) Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm* 56:1427–1432
- Fransman W, Vermeulen R, Kromhout H (2004) Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. *Ann Occup Hyg* 48:237–244
- Goloni-Bertollo EM, Tajara EH, Manzato AJ, Varella-Garcia M (1992) Sister chromatid exchanges and chromosome aberrations in lymphocytes of nurses handling antineoplastic drugs. *Int J Cancer* 50:341–344
- Hornung RW, Reed LD (1990) Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg* 5:46–51
- Kromhout H, Hoek F, Uitterhoeve R, Huijbers R, Overmars RF, Anzion R, Vermeulen R (2000) Postulating a dermal pathway for exposure to anti-neoplastic drugs among hospital workers. Applying a conceptual model to the results of three workplace surveys. *Ann Occup Hyg* 44:551–560
- Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K (2003) Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. *Ann Occup Hyg* 47:681–685
- McDevitt JJ, Lees PS, McDiarmid MA (1993) Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med* 35:57–60
- Milkovic-Kraus S, Horvat D (1991) Chromosomal abnormalities among nurses occupationally exposed to antineoplastic drugs. *Am J Ind Med* 19:771–774
- Minoia C, Turci R, Sottani C, Schiavi A, Perbellini L, Angeleri S, Draicchio F, Apostoli P (1998) Application of high performance liquid chromatography/tandem mass spectrometry in the environmental and biological monitoring of health care personnel occupationally exposed to cyclophosphamide and ifosfamide. *Rapid Commun Mass Spectrom* 12:1485–1493
- Pohlová H, Cerná M, Rössner P (1986) Chromosomal aberrations, SCE and urine mutagenicity in workers occupationally exposed to cytostatic drugs. *Mutat Res* 174:213–217
- Sardas S, Gök S, Karakaya AE (1991) Sister chromatid exchanges in lymphocytes of nurses handling antineoplastic drugs. *Toxicol Lett* 55:311–315
- Selevan SG, Lindbohm ML, Hornung RW, Hemminki K (1985) A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med* 313:1173–1178
- Sessink PJM, Anzion RBM, van den Broek PHH, Bos RP (1992a) Detection of contamination with anti-neoplastic agents in a hospital pharmacy department. *Pharmaceutisch Weekblad* 14:16–22

- Sessink PJM, Boer KA, Scheefhals APH, Anzion RBM, Bos RP (1992b) Occupational exposure to antineoplastic agents at several departments in a hospital. *Int Arch Occup Environ Health* 64:105–112
- Sessink PJM, Scholtes MM, Anzion RBM, Bos RP (1993) Determination of cyclofosfamide in urine by gas chromatography-mass spectrometry. *J Chromatogr B Biomed Appl* 616:333–337
- Sessink PJ, Cerna M, Rossner P, Pastorkova A, Bavarova H, Frankova K, Anzion RB, Bos RP (1994a) Urinary cyclophosphamide excretion and chromosomal aberrations in peripheral blood lymphocytes after occupational exposure to antineoplastic agents. *Mutat Res* 309:193–199
- Sessink PJ, van de Kerkhof MC, Anzion RB, Noordhoek J, Bos RP (1994b) Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health* 49:165–169
- Sessink PJ, Kroese ED, van Kranen HJ, Bos RP (1995) Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide. *Int Arch Occup Environ Health* 67:317–323
- Sessink PJ, Wittenhorst BC, Anzion RB, Bos RP (1997) Exposure of pharmacy technicians to antineoplastic agents: reevaluation after additional protective measures. *Arch Environ Health* 52:240–244
- van Strien RT, Verhoeff AP, Brunekreef B, Van Wijnen JH (1994) Mite antigen in house dust: relationship with different housing characteristics in The Netherlands. *Clin Exp Allergy* 24:843–853
- Stücker I, Caillard JF, Collin R, Gout M, Poyen D, Hemon D (1990) Risk of spontaneous abortion among nurses handling antineoplastic drugs. *Scand J Work Environ Health* 16:102–107
- Waksvik H, Klepp O, Brogger A (1981) Chromosome analyses of nurses handling cytostatic agents. *Cancer Treat Rep* 65:607–610